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(54) Title: THE USE OF BACTERIAL PHAGE ASSOCIATED LYSING ENZYMES FOR THE PROPHYLACTIC AND THERAPEUTIC TREATMENT OF VARIOUS ILLNESSES

(57) Abstract: A method for the prophylactic and therapeutic treatment of bacterial infections is disclosed which comprises the treatment of an individual with an effective amount of a modified version of a lytic enzyme produced by a bacteria infected with a bacteriophage specific for said bacteria wherein said modified version of said at least one lytic enzyme is selected from the group consisting of shuffled lytic enzymes, chimeric lytic enzymes, wherein the lytic enzyme is in an environment having a pH which allows for activity of said lytic enzyme; and a carrier for delivering said lytic enzyme. Additionally, a holin enzyme for puncturing the membrane may be included in the composition. This method, and composition can be used for the treatment of upper respiratory infections, skin infections, wounds, and burns, vaginal infections, eye infections, intestinal disorders and dental problems.

gum or lozenge. Any other carrier can be used that allows for the exposure of the mouth, gums, and teeth to the lytic enzyme.

The lytic enzyme may also be incorporated in a lyophilized or dried form in tooth powder. If the lytic enzyme is to be used in an oral wash, it is preferred that the oral wash not contain any alcohol, so as to not denature the enzyme. The enzyme can also be in a liposome when mixed in with the toothpaste or oral wash. The concentrations of the enzyme units per ml of toothpaste or mouth wash can be in the range of from about 100 units/ml to about 500,000 units/ml of composition, preferably in the range of about 1000 units/ml to about 100,000 units/ml, and most preferably from about 10,000 to 100,000 units/ml. The pH of the toothpaste or oral wash should be in a range that allows for the optimum performance of the enzyme, while not causing any discomfort to the user of the toothpaste or oral wash.

Many modifications and variations of the present invention are possible in light of the above teachings. It is, therefore, to be understood within the scope of the appended claims the invention may be protected otherwise than as specifically described.

What we claim is:

1) A method for the prophylactic or therapeutic treatment of bacterial infections, comprising:

administering an effective amount of at least one lytic enzyme produced by a bacteria infected with a bacteriophage specific for said bacteria to the site of the infection.

2) The method according to claim 1, further comprising delivering said lytic enzyme in a carrier suitable for delivering said lytic enzyme to the site of the infection.

3) The method according to claim 1, wherein the at least one lytic enzyme is for the treatment of *Hemophilus* influenza.

4) The method according to claim 1, wherein the at least one lytic enzyme is for the treatment of *Pseudomonas*.

5) The method according to claim 1, wherein the at least one lytic enzyme is for the treatment of *Streptococcus pneumoniae*

6) The method according to claim 1, wherein the at least one lytic enzyme is for the treatment of *Streptococcus fasciae*

7) The method according to claim 1, wherein the at least one lytic enzyme is for the treatment of *Listeria*.

8) The method according to claim 1, wherein the at least one lytic enzyme is for the treatment of *Salmonella*.

9) The method according to claim 1, wherein the at least one lytic enzyme is for the treatment of *E. coli*.

10) The method according to claim 1, wherein the at least one lytic enzyme is for the treatment of *Campylobacter*.

11) The method according to claim 1, wherein the at least one lytic enzyme is for the treatment of *Pseudomonas*.

12) The method according to claim 1, wherein the at least one lytic enzyme is for the treatment of *Streptococcus mutans*.

13) The method according to claim 1, wherein the at least one lytic enzyme is for the treatment of *Mycobacterium tuberculosis*.

14) The method according to claim 1, wherein the at least one lytic enzyme is for the treatment of *Streptococcus*.

15) The method according to claim 2, wherein the carrier is an inhalant.

16) The method according to claim 2, wherein the carrier is a topical cream

17) The method according to claim 2, wherein the carrier is a nasal spray.

18) The method according to claim 2, wherein the carrier is a syrup.

19) The method according to claim 2, wherein the carrier is a tablet.

20) The method according to claim 2, wherein the carrier is a tampon.

21) The method according to claim 2, wherein the carrier is a suppository.

22) The method according to claim 2, wherein the carrier is an eye drop solution.

23) The method according to claim 2, wherein the carrier is a candy.

24) The method according to claim 2, wherein the carrier is a chewing gum.

25) The method according to claim 2, wherein the carrier is a lozenge.

26) The method according to claim 2, wherein the carrier is a troche.

27) The method according to claim 2, wherein the carrier is a powder.

28) The method according to claim 2, wherein the carrier is an aerosol.

29) The method according to claim 2, wherein the carrier is a liquid.

30) The method according to claim 2, wherein the carrier is a liquid spray.

31) The method according to claim 2, wherein the carrier is a bandage.

32) The method according to claim 2, wherein the carrier is a toothpaste.

33) The method according to claim 2, wherein the carrier is an oral wash.

34) A method for the prophylactic and therapeutic treatment of bacterial infections of an upper respiratory tract, comprising administering a composition comprising an effective amount of at least one lytic enzyme produced by a bacteria infected with a bacteriophage specific for said bacteria to a mouth, throat, or nasal passage of a mammal.

35) The method according to claim 34, further comprising delivering said lytic enzyme in a carrier suitable for delivering said lytic enzyme to the mouth, the throat or the nasal passage.

36) The method according to claim 34, wherein said bacteria being treated is selected from the group consisting of *Streptococcus pneumoniae* and *Hemophilus influenza*.

37) The method according to claim 36, wherein said bacteria being treated is *Streptococcus pneumoniae*.

38) The method according to claim 36, wherein said bacteria being treated is *Hemophilus influenza*.

39) The method according to claim 34, wherein said carrier is a candy, chewing gum, lozenge, troche, tablet, a powder, an aerosol, a liquid and a liquid spray.

40) The method according to claim 34, wherein said composition further comprises a buffer that maintains pH of the composition at a range between about 4.0 and about 9.0.

41) The method according to claim 40, wherein the buffer maintains the pH of the composition at the range between about 5.5 and about 7.5.

42) The method according to claim 40, wherein said buffer comprises a reducing reagent.

43) The method according to claim 42, wherein said reducing reagent is dithiothreitol.

44) The method according to claim 40, wherein said buffer comprises a metal chelating reagent.

45) The method according to claim 44, wherein said metal chelating reagent is ethylenediaminetetracetic disodium salt.

46) The method according to claim 40, wherein said buffer is a citrate-phosphate buffer.

47) The method according to claim 34, further comprising a bactericidal or bacteriostatic agent as a preservative.

48) The method according to claim 34, wherein said at least one lytic enzyme is lyophilized.

49) The method according to claim 35, wherein said carrier further comprises a sweetener.

50) The method according claim 34, further comprising administering a concentration of about 100 to about 100,000 active enzyme units per milliliter of fluid in the wet environment of the nasal or oral passages.

51) The method according to claim 50, further comprising administering the concentration of about 100 to about 10,000 active enzyme units per milliliter of fluid in the wet environment of the nasal or oral passages.

52) The method according to claim 34, further comprising using said composition in the therapeutic treatment of *Streptococcus* infections.

53) The method according to claim 34, further comprising using said composition in the prophylactic treatment of *Streptococcus* infections.

54) The method according to claim 34, further comprising using said composition in the therapeutic treatment of *Streptococcus* infections.

55) The method according to claim 34, further comprising using said composition in the prophylactic treatment of *Hemophilus* infections.

56) The method according to claim 34, further comprising using said composition in the therapeutic treatment of *Hemophilus* infections.

57) A composition for use in the therapeutic or prophylactic treatment of a bacterial infection of an upper respiratory tract, comprising:

an effective amount of at least one lytic enzyme produced by a bacteria being infected with a bacteriophage specific for said bacteria; and

a carrier for delivering said at least one lytic enzyme to a mouth, throat, or nasal passage.

58) The composition according to claim 57, wherein said bacteria being treated is selected from the group consisting of *Streptococcus pneumoniae* and *Hemophilus influenza*.

59) The composition according to claim 58, wherein said bacteria being treated is *Streptococcus pneumoniae*.

60) The composition according to claim 58, wherein said bacteria being treated is *Hemophilus influenza*.

61) The composition according to claim 57, wherein said carrier is selected from the group consisting of a candy, chewing gum, lozenge, troche, tablet, a powder, an aerosol, a liquid and a liquid spray.

62) The composition according to claim 57, wherein said composition further comprises a buffer that maintains pH of the composition at a range between about 4.0 and about 9.0.

63) The composition according to claim 62, wherein the buffer maintains the pH of the composition at the range between 5.5 and 7.5.

64) The composition according to claim 62, wherein said buffer comprises a reducing reagent.

65) The composition according to claim 64, wherein said reducing reagent is dithiothreitol.

66) The composition according to claim 62, wherein said buffer comprises a metal chelating reagent.

67) The composition according to claim 66, wherein said metal chelating reagent is ethylenediaminetetracetic disodium salt.

68) The composition according to claim 62, wherein said buffer is a citrate-phosphate buffer.

69) The composition according to claim 57, further comprising a bactericidal or bacteriostatic agent as a preservative.

70) The composition according to claim 57, wherein said lytic enzyme is lyophilized.

71) The composition according claim 57, wherein said at least one lytic enzyme is present in a concentration of about 100 to about 100,000 active

enzyme units per milliliter of fluid in the wet environment of the nasal or oral passages.

72) The composition according to claim 71, wherein said at least one lytic enzyme is present in a concentration of about 100 to about 10,000 active enzyme units per milliliter of fluid in the wet environment of the nasal or oral passages.

73) A method for the treatment of bacterial infections of the digestive tract, comprising administering to the digestive tract a composition comprising an effective amount of at least one lytic enzyme produced by a bacteria infected with a bacteriophage specific for said bacteria.

74) The method according to claim 73, further comprising delivering said lytic enzyme in a carrier suitable for delivering said lytic enzyme to the digestive tract.

75) The method for the treatment of bacterial infections according to claim 73, wherein said gram negative bacterial infections are caused by bacteria selected from the group consisting of *Listeria*, *Salmonella, E. coli*, and *Campylobacter*.

76) The method for the treatment of bacterial infections according to claim 73, wherein said carrier is selected from the group consisting of suppository enemas, syrups, and enteric coated pills.

77) A composition for treating for the treatment of bacterial infections of the digestive tract, comprising an effective amount of at least one lytic enzyme produced by said bacteria being infected with a bacteriophage specific for said bacteria, and

a carrier for delivering said lytic enzyme to the digestive tract.

78) The composition according to claim 77, wherein said bacteria to be treated are selected from the group consisting of *Listeria*, *Salmonella*, *E. coli*, and *Campylobacter*.

79) The composition according to claim 77, wherein said carrier for delivering said at least one lytic enzyme to the digestive tract is selected from the group consisting of suppository enemas, syrups, or enteric coated pills.

80) The composition of claim 77, wherein said composition further comprises a buffer that maintains pH of the composition at a range between about 4.0 and 9.0.

81) The composition according to claim 80, wherein the buffer maintains the pH of the composition at the range between 5.5 and 7.5.

82) The composition according to claim 80, wherein said buffer comprises a reducing reagent.

83) The composition according to claim 82, wherein said reducing reagent is dithiothreitol.

84) The composition according to claim 80, wherein said buffer comprises a metal chelating reagent.

85) The composition according to claim 84, wherein said metal chelating reagent is ethylenediaminetetracetic disodium salt.

86) The composition according to claim 80, wherein said buffer is a citrate-phosphate buffer.

87) The composition according to claim 77, further comprising a bactericidal or bacteriostatic agent as a preservative.

88) The composition according to claim 77, wherein said at least one lytic enzyme is lyophilized.

89) The composition according claim 77, wherein said at least one lytic enzyme is present in a concentration of about 100 to about 100,000 active enzyme units per milliliter of fluid in the wet environment of the digestive tract

90) The composition according to claim 89, wherein said at least one lytic enzyme is present in a concentration of about 100 to about 10,000 active enzyme units per milliliter of fluid in the wet environment of the digestive tract.

91) A composition for the therapeutic or prophylactic treatment of bacterial infections of burns and wounds of the skin, comprising:

an effective amount of at least one lytic enzyme produced by a bacteria infected with a bacteriophage specific for said bacteria; and

a carrier for delivering said at least one lytic enzyme to the skin.

92) The composition according to claim 91, wherein said carrier is a bandage.

93) The composition according to claim 91, further comprising using said composition in the prophylactic treatment of bacterial infections.

94) The composition according to claim 91, further comprising using said composition in the therapeutic treatment of bacterial infections.

95) The composition according to claim 91, wherein said bacteria being treated is *Pseudomonas*.

96) The composition according to claim 95, wherein said lytic enzyme is produced by the *Pseudomonas* bacteria being infected with a bacteriophage specific for the *Pseudomonas*.

97) The composition according to claim 86, wherein said bacteria being treated is *Staphylococcus*.

98) The composition according to claim 97, wherein said lytic enzyme is produced by the *Staphylococcus* bacteria being infected with a bacteriophage specific for the *Staphylococcus*.

99) The composition according to claim 91, wherein said bacterium being treated are *Staphylococcus* and *Pseudomonas*.

100) The composition according to claim 99, wherein said lytic enzymes are produced by the *Staphylococcus* bacteria being infected with a bacteriophage specific for the *Staphylococcus*, and *Pseudomonas* bacteria being infected with a bacteriophage specific for the *Pseudomonas*.

101) A method for the therapeutic or prophylactic treatment of bacterial infections of burns and wounds of the skin, comprising:

administering to an infected area of the skin a composition comprising an effective amount of a lytic enzyme produced by a bacteria infected with a bacteriophage specific for said bacteria..

102) The method according to claim 101, further comprising delivering said lytic enzyme in a carrier suitable for delivering said lytic enzyme to the skin.

103) The method according to claim 102, wherein said carrier is a bandage.

104) The method according to claim 101, further comprising using said composition in the prophylactic treatment of bacterial infections.

105) The method according to claim 101, further comprising using said composition in the therapeutic treatment of bacterial infections.

106) The method according to claim 101, wherein said bacteria being treated is *Pseudomonas*.

107) The method according to claim 106, wherein said lytic enzyme is produced by the *Pseudomonas* bacteria being infected with a bacteriophage specific for the *Pseudomonas*.

108) The method according to claim 101, wherein said bacteria being treated is *Staphylococcus*.

109) The method according to claim 108, wherein said lytic enzyme is produced by the *Staphylococcus* bacteria being infected with a bacteriophage specific for the *Staphylococcus*.

110) The method according to claim 101, wherein said bacterium being treated are *Staphylococcus* and *Pseudomonas*.

111) The method according to claim 110, wherein said lytic enzymes are produced by the *Staphylococcus* bacteria being infected with a bacteriophage specific for the *Staphylococcus*, and *Pseudomonas* bacteria being infected with a bacteriophage specific for the *Pseudomonas*.

112) A method for the prophylactic and therapeutic treatment of vaginal infections, comprising:

administering to the vagina composition comprising an effective amount of at least one lytic enzyme produced by said bacteria being infected with a bacteriophage specific for said bacteria.

113) The method according to claim 112, further comprising delivering said lytic enzyme in a carrier suitable for delivering said lytic enzyme to the vagina.

114) The method according to claim 113, wherein said carrier to be placed in the vagina.

115) The method according to claim 113, wherein said carrier is a tampon.

116) The method according to claim 113, wherein said carrier is a pad.

117) The method according to claim 113, wherein said carrier is a douche.

118) The method according to claim 112, wherein said lytic enzyme is specific for Group B *Streptococcus*.

119) A composition for the prophylactic and therapeutic treatment of treatment of vaginal infections, comprising:

an effective amount of at least one lytic enzyme produced by said bacteria being infected with a bacteriophage specific for said bacteria; and

a carrier for delivering said lytic enzyme to a vagina.

120) The composition according to claim 119, wherein said carrier is a tampon.

121) The composition according to claim 119, wherein said carrier is a douche.

122) The composition according to claim 119, wherein said carrier is a pad.

123) The composition according to claim 119, wherein said lytic enzyme is specific for Group B *Streptococcus*.

124) A method for the prophylactic and therapeutic treatment of eye infections, comprising:

administering to an eye a composition comprising an effective amount of at least one lytic enzyme produced by said bacteria being infected with a bacteriophage specific for said bacteria.

125) The method according to claim 124, further comprising delivering said lytic enzyme in a carrier suitable for delivering said lytic enzyme to the eye.

126) The method according to claim 124, wherein said bacteria being treated is *Hemophilus*.

127) The method according to claim 124, wherein said bacteria being treated is *Staphylococcus*.

128) The method according to claim 125, wherein the carrier is an eye drop solution.

129) The method according to claim 125, wherein the carrier is an eye wash solution.

130) The method according to claim 128, wherein said solution is an isotonic solution.

131) A composition for use in the therapeutic or prophylactic treatment of an eye infection,, comprising:

an effective amount of at least one lytic enzyme produced by bacteria being infected with a bacteriophage specific for said bacteria; and

a carrier for delivering said lytic enzyme to the eye.

132) The composition according to claim 131, wherein said bacteria being treated is *Hemophilus*.

133) The composition according to claim 131, wherein said bacteria being treated is *Staphylococcus*.

134) The composition according to claim 131, wherein said carrier is an isotonic solution.

135) The composition according to claim 134, wherein said isotonic solution is in an eye drop dispenser.

136) A method for the prophylactic or therapeutic treatment of dermatological infections comprising:

topically applying to an infected area of the skin a composition comprising an effective amount of at least one lytic enzyme produced by bacteria infected with a bacteriophage specific for said bacteria..

137) The method according to claim 136, further comprising delivering said composition in a pharmaceutically acceptable carrier.

138) The method according to claim 137, wherein said carrier is selected from the group consisting of an aqueous liquid, an alcohol base, a water soluble gel, a lotion, an ointment, a nonaqueous liquid base, a mineral oil base, a blend of mineral oil and petrolatum, lanolin, liposomes, hydrophilic gelling agents, cross-linked acrylic acid polymers (carbomer), cellulose polymers, hydroxy ethyl

cellulose, cellulose gum, MVE/MA decadiene crosspolymers, PVM/MA copolymers, and any combinations thereof.

139) The method according to claim 136, wherein the form in which the composition is delivered is selected from the group consisting of a spray, a smear, a time release patch, a liquid absorbed wipe, and any combinations thereof.

140) The method according to claim 136, wherein the lytic enzyme is in an environment having a pH which allows for activity of said lysin enzyme.

141) The method according to claim 140, wherein said composition further comprises a buffer that maintains pH of the composition at a range between about 4.0 and about 9.0.

142) The method according to claim 141, wherein said buffer maintains the pH of the composition at the range of between about 5.5 and about 7.5.

143) The method according to claim 141, wherein said buffer comprises a reducing agent.

144) The method according to claim 143, wherein said reducing agent is dithiothreitol.

145) The method according to claim 131, wherein said composition further comprises a mild surfactant in an amount effective to potentiate effects of the lytic enzyme.

146) The method according to claim 131, wherein the composition further comprises at least one complementary agent which potentiates the bactericidal

activity of the lytic enzyme, said complementary agent being selected from the group consisting of penicillin, synthetic penicillins bacitracin, methicillin, cephalosporin, polymyxin, cefaclor. Cefadroxil, cefamandole nafate, cefazolin, cefixime, cefmetazole, cefonioid, cefoperazone, ceforanide, cefotanme, cefotaxime, cefotetan, cefoxitin, cefpodoxime proxetil, ceftazidime, ceftizoxime, ceftriaxone, cefriaxone moxalactam , cefuroxime, cephalexin, cephalosporin C, cephalosporin C sodium salt, cephalothin, cephalothin sodium salt, cephapirin, cephradine, cefuroximeaxetil, dihydratecephalothin, moxalactam, loracarbef. mafate and chelating agents in an amount effective to synergistically enhance effects of the lytic enzyme.

147) The method according to claim 136, wherein the composition further comprises lysostaphin for the treatment of any *Staphylococcus aureus* bacteria.

148) The method according to claim 136, wherein said lytic enzyme is present in an amount ranging from about 100 to about 500,000 units per milliliter.

149) A composition for the treatment of dermatological *Streptococcus* infections comprising:

an effective amount of at least one lytic enzyme produced by bacteria infected with a bacteriophage specific for said bacteria and a carrier for topical application of the at least one lytic enzyme.

150) The composition according to claim 149, wherein said carrier is selected from the group consisting of an aqueous liquid, an alcohol base, a water soluble gel, a lotion, an ointment, a nonaqueous liquid base, a mineral oil base, a blend of mineral oil and petrolatum, lanolin, liposomes, hydrophilic gelling agents, cross-linked acrylic acid polymers (carbomer), cellulose polymers, hydroxy ethyl cellulose, cellulose gum, MVE/MA decadiene crosspolymers, PVM/MA copolymers, and any combinations thereof.

151) The composition according to claim 150, wherein said composition is in the form selected from the group consisting of a spray, a smear, a time release patch, a liquid absorbed wipe, and any combinations thereof.

152) The composition according to claim 149, wherein the at least one lytic enzyme is in an environment having a pH which allows for activity of said lytic enzyme.

153) The composition according to claim 149, wherein said composition further comprises a buffer that maintains pH of the composition at a range between about 4.0 and about 9.0.

154) The composition according to claim 153, wherein said buffer maintains the pH of the composition at the range of between about 5.5 and about 7.5.

155) The composition according to claim 153, wherein said buffer comprises a reducing agent.

156) The composition according to claim 149, wherein said reducing agent is dithiothreitol.

157) The composition according to claim 153, wherein said buffer comprises a metal chelating reagent.

158) The composition according to claim 149, further comprising a bactericidal or bacteriostatic agent as a preservative.

159) The composition according to claim 149, further comprising a surfactant in an amount effective to potentiate a therapeutic effect of the composition.

160) The composition according to claim 149, wherein the composition further comprises at least one complementary agent which potentiates the bactericidal activity of the lytic enzyme, said complementary agent being selected from the group consisting of penicillin, synthetic penicillins bacitracin, methicillin, cephalosporin, polymyxin, cefaclor. Cefadroxil, cefamandole nafate, cefazolin, cefixime, cefmetazole, cefonioid, cefoperazone, ceforanide, cefotanme, cefotaxime, cefotetan, cefoxitin, cefpodoxime proxetil, ceftazidime, ceftizoxime, ceftriaxone, cefriaxone moxalactam , cefuroxime, cephalexin, cephalosporin C, cephalosporin C sodium salt, cephalothin, cephalothin sodium salt, cephapirin, cephradine, cefuroximeaxetil, dihydratecephalothin, moxalactam, loracarbef. mafate chelating agents, and combinations thereof in an amount effective to synergistically enhance the therapeutic effect of the lytic enzyme.

161) The composition according to claim 149, wherein the composition further comprises lysostaphin for the treatment of any *Staphylococcus aureus* bacteria.

162) The composition according to claim 149, wherein the composition further comprises lysozyme.

163) The composition according to claim 149, further comprising at least one emulsifier.

164) The composition according to claim 149, further comprising at least one antioxidant.

165) The composition according to claim 149, further comprising at least one sunscreen.

166) The composition according to claim 149, further comprising at least one preservative.

167) The composition according to claim 149, further comprising at least one anti-inflammatory agent.

168) A composition for the therapeutic or prophylactic treatment of bacterial infections of the upper respiratory system, comprising an effective amount of at least one lytic enzyme produced by bacteria infected with a bacteriophage specific for that bacteria and a pharmaceutically acceptable carrier in an inhaler allowing for the administration of the at least one lytic enzyme to the bronchial tubes and lungs.

169) The composition according to claim 168, wherein said composition is for the therapeutic treatment of bacterial infections of the upper respiratory system.

170) The composition according to claim 168, wherein said composition is for the prophylactic treatment of bacterial infections of the upper respiratory system.

171) A composition for the therapeutic or prophylactic treatment of bacterial infections of the mouth or teeth, comprising an effective amount of at least one lytic enzyme produced by bacteria infected with a bacteriophage specific for that bacteria and a pharmaceutically acceptable carrier for topical application of the at least one lytic enzyme.

172) The composition according to claim 171, wherein in said composition is for the treatment of dental caries.

173) The composition according to claim 172, wherein said composition is used for the prophylactic treatment of dental caries.

174) The composition according to claim 172, wherein said composition is used for the therapeutic treatment of dental caries.

175) The composition according to claim 171, wherein said carrier is toothpaste.

176) The composition according to claim 171, wherein said carrier is an oral wash.

177) The composition according to claim 171, wherein said carrier is a chewing gum.

178) The composition according to claim 171, wherein said carrier is a lozenge.

179) The composition according to claim 171, wherein said bacteria being treated is *Streptococcus mutans*.

180) The composition according to claim 171, wherein said lytic enzyme is present in an amount ranging from about 100 to about 500,000 units per milliliter.

181) The composition according to claim 180, wherein said lytic enzyme is present in an amount ranging from about 10,000 to about 100,000 units per milliliter.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/04063

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 38/44, 38/47; G01N 33/569; C12N 9/14, 9/36

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/7.29, 34, 30, 36, 195, 206, 961, 962, 975; 424/94.1; 94.6, 94.61; 436/518, 524, 531, 533, 536, 808

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X - Y	US 5,604,109 A (FISCHETTI et al.) 18 February 1997, see entire document.	1-9,11, 15-17 -------- 10, 12-14, 18-31
Y	US 3,852,424 A (GAEUMANN et al.) 03 December 1974, see entire document, particularly, col. 12, line 62 through col. 13, line 7.	1-31

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 03 MAY 1999	Date of mailing of the international search report 21 JUN 1999
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/04063

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

435/7. 29, 34, 30, 36, 195, 206, 961, 962, 975; 424/94.1; 94.6, 94.61; 436/518, 524, 531, 533, 536, 808

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS, JPOABS, EPOABS, CAPLUS, BIOSIS, MEDLINE, AGRICOLA
search terms: streptococc?, page associated lysin?; carrier, nose or nasal, throat, mouth, oral; spray, ointment, liquid, aerosol; gum